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(54) Titre : MEDICAMENTS A BASE DE PLANTES SERVANT A ACCROITRE LE TONUS ET A MODULER LE TONUS D'ORGANES MUSCULAIRES LISSES

(54) Title: PLANT-BASED MEDICAMENTS FOR INCREASING THE TONE AND MODULATING THE TONE OF THE SMOOTH MUSCULAR ORGANS

(57) Abrégé/Abstract:
Plant-based medicament having tonicising action on smooth muscular organs which are atonic or have decreased tone. It contains Iberis amara, preferably Iberis amara totalis (flowers, seeds, leaves, stalk and roots), in particular as a plant extract or its constituents, as the sole carrier of the activity.

Abstract

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Plant-based medicament having tonicising action on smooth muscular organs which are atonic or have decreased tone. It contains Iberis amara, preferably Iberis amara totalis (flowers, seeds, leaves, stalk and roots), in particular as a plant extract or its constituents, as the sole carrier of the activity.

Sign. Fig. 1

Description

The invention relates to a plant-based medicament having tonicising action on smooth muscular organs which are atonic or have decreased tone. It furthermore relates to such a medicament having tone-modulating action on organs of this type which have decreased tone or increased tone. Finally, it is aimed at the use of a medicament of this type as a base therapeutic.

In gastroenterological diagnoses such as dyspepsia, functional gastrointestinal complaints, gastropathy and irritable colon, with complex and diverse symptoms, tone-related incorrect regulation of the gastrointestinal motor system or motility is important. Both cramps (spasms) and also hypotonic constipation (atonia) with decreased gastrointestinal emptying occur, accompanied by such disorders as pressure and pain in the upper abdomen, gastrocardiac pain, eructation, heartburn, sensation of fullness, oesophagitis and gastritis and even ulcers in the gastrointestinal tract.

In therapy, the chemical medicaments known are mainly those which have a spasmolytic anticholinergic effect or the chemical prokinetics and dopamine antagonists, which have side effects. A plant-based medicament is also known. The plant constituents it contains are compulsorily a mixture of Iberis amara totalis, alcoholic fresh plant extract, together with alcoholic drug extracts of Angelicae radix, Cardui mariae fructus, Carvi fructus, Chelidonii herba, Liquiritae radix, Matricariae flos, Melissae folium and Menthae piperitae folium. There are therefore a relatively large number of active substances which the patient is forced to take.

The object of the invention is to provide a plant-based medicament having a limited number of active substances/constituents, in particular extracts, which has a fundamentally tone-increasing effect in the relaxed smooth musculature, in particular of the intestine.

This object is achieved according to the invention in that the medicament contains Iberis amara, preferably Iberis amara totalis (flowers, seeds, leaves, stalk and roots), in particular as a plant extract, as the sole carrier of the activity. It has surprisingly been shown that the active substances of this plant suffice, without any other assistance and active substances, both in the prophylactic and therapeutic respect for increasing the tone and motility in hypotonic smooth muscular organs, such as the gastrointestinal tract, gall bladder, urinary bladder, veins and uterus. The additional plant active substances previously held as necessary for achieving this action are thus unnecessary, and there is thus a substantially lower load on the patient than when the known medicaments are taken.

In continuation of the invention, it has also surprisingly been found that a plant-based medicament having tone-modulating action on smooth muscular organs which have decreased tone or increased tone is provided when, besides Iberis amara, preferably Iberis amara totalis (flowers, seeds, leaves, stalk and roots), in particular as a plant extract, it contains one or more other constituents of the group consisting of Menthae piperitae folium, Matricariae flos, Carvi fructus, Melissae folium and Liquiritiae radix, preferably as a plant extract, as the sole carrier of the activity. This medicament according to the invention is distinguished from the abovementioned known plant-based medicaments in that in contrast it contains a reduced number of plant substances. Compared with the known medicaments, Chelidonii herba, Cardui maria fructus and Angelicae radix are not present. A whole series of, under certain circumstances, loading substances can be dispensed with

in the treatment of patients. In spite of this, the medicament according to the invention is completely effective in the propylactic and therapeutic respect for modulating or regulating the tone and motility in disorders of smooth muscular organs, such as the gastrointestinal tract, gall bladder, urinary bladder, veins and uterus, which disorders are of causal, or as a consequence of tone and motility disorders, various genesis. Besides Iberis amara totalis, the plants or their active substances used in the medicament according to the invention have, above all, a spasmolytic action and produce, in cooperation with Iberis amara, completely the desired effect of tone-modulating action on smooth muscular organs which have decreased tone or increased tone. The medicament according to the invention can be used both as a primary (causal) or secondary therapeutic, in particular in complaints of the gastrointestinal tract having the tone and motility disorders mentioned, both in hypotonic and hypertonic and in hypokinetic and hyperkinetic states.

According to the invention, it is furthermore intended that the medicament is prepared in the form of plant extracts and consists essentially of

15 - 40 % by volume of Iberis amara,
10 - 30 % by volume of Menthae piperitae,
20 - 40 % by volume of Matricariae,
10 - 30 % by volume of Carvi fructus,
10 - 30 % by volume of Melissae folium and
10 - 30 % by volume of Liquiritiae radix.

A particularly preferred exemplary embodiment of the invention is distinguished in that the plant extracts are intended to be as follows:

15 % by volume of Iberis amara totalis,
10 % by volume of Menthae piperitae folium,
30 % by volume of Matricariae flos,
20 % by volume of Carvi fructus,
15 % by volume of Melissae folium and
10 % by volume of Liquiritiae radix.

It is also within the scope of the invention if the plant extract, preferably Iberis amara, is a fresh plant extract. As a result of this, a number of active substances are added to the medicament which, in the preparation of a drug extract, could in certain circumstances be no longer completely present and thus no longer active. Even with the other plants present in the manner according to the invention in a reduced number compared with the prior art, fresh plant extracts can be prepared, although as a rule drug extracts are prepared from these plants.

According to the invention, in the fresh plant extract the ratio of macerated or percolated plants to the extracts is about 3 to 7, preferably 6 grams of Iberis amara : 10 grams. In the drug extract, according to the invention a ratio of drugs to extract of about 1.5 to 10 : preferably 3.5 grams : 10 grams is envisaged. According to the invention, the extracting agent preferably used for the extracts is ethanol in a final concentration of 30 to 40 % by volume, the remainder being H_2O.

Finally, it is within the scope of the invention to use the medicament according to the invention as a base therapeutic.

To summarise, it can be stressed that it has surprisingly been found that the medicament according to the invention according to Claim 1 and according to Claims 2 to 4 is just as active as and, in a particular respect, even more active than the medicament available on the market until now (STW 5), which - compared with the medicament according to the invention according to Claims 2 to 4 - additionally contains Chelidonii herba, Cardui mariae fructus and Angelicae radix.

The functional gastrointestinal complaints are multifactorial occurrences in which the medicament according to the invention intervenes multifocally and accordingly, as further shown below, has been tested.

Other details, features and advantages of the invention will emerge from the following description, the patent claims and the drawing, in which:

Fig. 1 shows the effect of the medicament according to the invention according to Claim 1 on the tone of resting isolated guinea-pig ileum;

Fig. 2 shows the graphical representation of Table 2;

Fig. 3 shows the graphical representation of Table 3;

Figs. 4 to 7 show the effect of the medicament according to the invention according to Claim 2 and a comparison of the effect of the medicament according to the invention according to Claim 2 compared with the known plant-based medicament (STW 5) on histamine-induced contraction (spasms) of the guinea-pig ileum at the different concentrations indicated.

Increase in tone

The effect of Iberis amara fresh plant extract according to Claim 1, called STW 6 in the text which follows, on the tone of the intestine was tested using the classical pharmacological guinea-pig ileum model according to Magnus, R.: Versuche am überlebenden Dünndarm von Säugetieren, Ist communication, Pflügers Archiv Ges. Physiol. 102, 123-151 (1904), both on a resting and on an acetylcholine-stimulated piece of ileum in a 37°C thermostated organ bath containing Krebs-Henseleit base solution with 95% O_2/5% CO_2 aeration.

STW 6 led in the resting/relaxed (atonic) guinea-pig ileum to a dose-dependent increase in basal tone (Fig. 1), and additionally to a fully reversible spontaneous contraction.

In an intestine stimulated with only a low acetylcholine concentration (2.5 - 160 µg/l) (hypotonic state), STW 6 likewise causes a dose-dependent increase in tone. At higher acetylcholine doses (> 160 - 640 µg/l), at which adequate tone and contraction prevail, STW 6 no longer has a tone-increasing action.

Motility of the gastrointestinal tract (fresh plant extracts)

Investigations of the effect of Iberis amara fresh plant extract on the motility of the gastrointestinal tract in minipigs from Alaska-Hoke (body weight around 20 - 25 kg) were furthermore carried out. Under Nembutal anaesthesia, the animals were subjected to endoscopy and the test substances were applied to the gastric mucosa under endoscopic viewing.

The motility was determined by means of a probe and timer. In addition, the following parameters were determined:

Acidity, according to Lanza, F.C.; Aspinall, R.L.; Swabb, E.A. et al.: A double-blind, placebo-controlled, endoscopic comparison of the cytoprotective effects of misoprostol and cimetidine in tolmetin-induced gastric mucosal injury. Clinical development of misoprostol: Peptic ulcer disease and NSAID induced gastropathy, Chicago, May 1987 and Davenport (1964), Tissue histamine, according to Lorenz, W.; Reimann, H.-J. et al.: A sensitive and specific method for the determination of histamine in human whole blood and plasma. Hoppe-Seyler's Z. Physiol. Chem. 353, 911-920 (1972), Mast cells, according to Mohri, K.; Reimann, H.-J. et al.: Histamine content and mast cells in human gastric and duodenal mucosa. Agents and Actions 8 (4), 372 (1978) and Prostaglandin (PGE_2), according to Moncada, S.; Herman, A.G. et al.: Differential formation of prostacyclin (PGX or PGI_2) by lysis of the arterial wall. An explanation for the anti-thrombotic properties of vascular endothelium. Thrombosis Research 11, 323 - 344 (1977).

The result of this investigation (Table 1) shows that Iberis amara increases the motility both of the stomach and of the intestine in a statistically significant manner. In addition, a cytoprotective action can be detected due to the statistically significant inhibition of acetylsalicylic acid-provoked tissue histamine release and mast cell proliferation.

The tone- and motility-regulating action of the medicament according to the invention according to Claims 2 to 9, also called STW 5-II, containing a decreased number of constituents suitable as carriers of the activity compared with the known plant-based product (STW 5) was investigated as follows:

Increase in basal tone

The basal tone-increasing action of STW 5-II compared with STW 5 was verified using the classical pharmacological model of the guinea-pig ileum according to Magnus. In Tables 2 and 3 and Figs. 2 and 3 respectively which represent them graphically, the results are presented compared with the contraction induced by acetylcholine, 40 µg/l.

The medicament according to the invention STW 5-II has a distinct basal tone-increasing effect in the hypotonic piece of intestine and has a stronger action than the known product (STW 5).

Spasmolytic action

The spasmolytic action of the medicament (STW 5-II) was investigated on histamine-induced contraction (spasms) of the guinea-pig ileum and compared with that of the known former product in the same ileum pieces.

The dose-response curves presented in Figs. 4 to 7 show that the medicament STW 5-II is effective in a dose-dependent and statistically significant spasmolytic (antispasmodic) manner against histamine-induced contraction of the guinea-pig ileum. This activity is comparable at all dosages with that of the former product, but with a distinctly decreased number of constituents.

Motility of the gastrointestinal tract (STW 5-II)

The action of the medicament according to the invention according to Claims 2 to 9 on the motility of the gastrointestinal tract was investigated in minipigs from Alaska-Hoke by the methods described previously. In addition to the determination of the motility of the stomach and of the intestine, pH, acidity, tissue

histamine, mast cells and prostaglandins (PGE_2) were measured before and after administration of the preparations.

From the results in Table 4 it can be inferred that the medicament combination according to Claims 2 to 9 increases the motility of the hypotonic stomach and of the intestine in a statistically significant manner. The histamine release and mast cell proliferation provoked by acetylsalicylic acid are also inhibited in a statistically significant manner as a sign of the anti-inflammatory and cytoprotective action.

A comparison of this effect with that of the known product (STW 5) (Table 5) makes it clear that the activity of the medicament according to Claims 1 to 9 is to be classified as significantly stronger.

Effect on the 5-Lipoxygenase products (LTB_4)

Both the prostaglandins (in particular PGE_2), cyclooxygenase products from the arachidonic acid cascade and the leukotrienes (LTB_4), the lipoxygenase metabolites, belong to the mediators of humoral inflammation whose inhibition would be highly desirable in ulcerating gastrointestinal dyspeptic disorders.

The effects on the 5-lipoxygenase products (LTB_4) by the medicament according to Claims 2 to 9 was measured by means of HPLC on activated polymorphonuclear, neutrophilic granulocytes of the rat in vitro after stimulation with calcium ionophore A23187.

If the amount produced in the control experiment is made equal to 100%, the following values are obtained in % $\bar{X}$ ± SD for the test substances:

			Inhibition
STW 5	:	89 ± 19	11 %
STW 6	:	96 ± 7	4 %
STW 5-II	:	75 ± 8	25 %

The action of the medicament according to Claims 2 to 9 in inhibition of the 5-lipoxygenase products is also stronger than that of the former product.

Anti-inflammatory action

The carrageenan oedema model of the rat is an internationally recognised pharmacological method for uncovering clinically relevant anti-inflammatory agents.

The test substances were administered 1/2 h before induction of oedema; the control animals received the solvent (30% ethanol). The paw volume was measured with a plethysmometer before (0 value) oedema induction and 1, 2, 3, 4 and 6 hours after.

The anti-inflammatory action of the test substances was calculated according to the formula

$$\% \text{ inhibition} = 100 - \left(\frac{V}{K} \cdot 100 \right)$$

V = average value of the differences from the 0 value: drug group
K = average value of the differences from the 0 value; control group

The following results were obtained (% inhibition):

	1	2	3	4	6 h
	- after oedema induction -				
STW 5 5 ml/kg of body wt.:	24.0	20.6	25.0*	37.5	38.7
STW 5-II 5 ml/kg of body wt.:	4.0	14.7	27.5*	35.0*	38.7*
Indomethacin 4 mg/kg of body wt.:	24.0	23.5	35.0*	47.5*	61.3*

* $P \leq 0.05$

The results show that the medicament according to Claim 1 or 2 has a statistically significant anti-inflammatory action in the critical inflammation phase

(3 to 6 hours after induction) and that this activity is of the order of magnitude of that of the former product and can be compared with that of the chemical substance indomethacin.

In addition to the dual action of tone/motility regulation, the medicament according to the invention has a distinct anti-inflammatory potential owing to inhibition of the cyclo- and lipoxygenase products which occur in dyspeptic or functional and motility-related gastrointestinal disorders due to damage to the mucous membranes (gastritis, colitis, ulcers and the like).

As a tone modulator, the plant-based medicament according to Claims 1 to 9 combines the advantages of a spasmolytic and a spasmodic (prokinetic) with the properties of an anti-inflammatory agent.

Table 1

Iberis Amara (STW 6) n = 6

	before	after	
pH	1.8 ± 0.1	1.6 ± 0.2	
Acidity	24 ± 4	26 ± 3	
Tissue histamine	33 ± 4	36 ± 4	
Provocation	34 ± 4	24 ± 2	**
Mast cells	---	62 ± 6	
Provocation	59 ± 3	45 ± 4	**
PGE_2	14 ± 3	13 ± 4	
Provocation	10 ± 2	10 ± 3	
Gastric motility	5 ± 3	8 ± 2	*
Intestinal motility	10 ± 4	14 ± 3	*

* = $p < 0.05$

** = $p < 0.005$

Table 2

Increase in basal tone

Test substance STW 5-11

Concentration (ml/l)	Expt. 1	Expt. 2	Expt. 3	Expt. 4	Expt. 5	Expt. 6
1.25	0.0	0.0	0.0	0.5	0.0	0.0
2.5	2.0	0.1	0.4	0.6	0.1	0.0
5.0	1.0	0.2	1.1	1.2	0.0	0.7
10.0	2.0	0.3	2.1	3.4	0.2	1.5
20.0	3.0	0.4	5.4	6.0	0.4	2.3
40.0	3.0	0.6	5.1	6.0	0.3	1.9
Acetylch. 40 µg/l	10.1	14.6	11.7	14.0	12.7	8.6

Average values

Concentration (ml/l)	Average value	SEM	Number
1.25	0.08	0.08	6
2.5	0.53	0.28	6
5.0	0.70	0.19	6
10.0	1.58	0.45	6
20.0	2.92	0.89	6
40.0	2.82	0.87	6
Acetylch. 40 µg/l	11.95	0.86	6

Table 3

Increase in basal tone

Test substance STW 5

Concentration (ml/l)	Expt. 1	Expt. 2	Expt. 3	Expt. 4	Expt. 5	Expt. 6
1.25	0.3	0.0	1.8	0.1	0.3	0.3
2.5	0.3	0.0	2.6	0.0	0.8	0.7
5.0	0.3	0.2	2.4	0.1	0.8	0.5
10.0	0.2	0.1	3.2	0.1	1.7	1.1
20.0	0.2	0.0	2.6	0.3	0.9	1.2
40.0	0.1	0.0	0.8	0.1	0.1	0.0
Acetylch. 40 µg/l	11.8	6.3	12.1	9.9	12.2	5.9

Average values

Concentration (ml/l)	Average value	SEM	Number
1.25	0.47	0.25	6
2.5	0.73	0.36	6
5.0	0.72	0.32	6
10.0	1.07	0.46	6
20.0	0.87	0.36	6
40.0	0.18	0.11	6
Acetylch. 40 µg/l	9.70	1.09	6

Table 4

Fol. Melissae
Fruct. Carvi
Flor. Chamomillae
Iberis amara
Fol. Menthae pip.

Combination STW 5-II n = 6

	before	after
pH	1.4 ± 0.2	2.2 ± 0.4
Acidity	22 ± 4	29 ± 5
Tissue histamine	32 ± 5	37 ± 6
Provocation	36 ± 6	30 ± 7 *
Mast cells	64 ± 6	61 ± 3
Provocation	68 ± 7	54 ± 6 *
PGE_2	10 ± 4	17 ± 3 **
Provocation	13 ± 4	12 ± 4
Gastric motility	5 ± 2	11 ± 3 **
Intestinal motility	10 ± 2	11 ± 3 **

Table 5

Known product (STW 5)

	before	after
pH	1.4 ± 0.3	1.9 ± 0.4
Acidity	26 ± 5	29 ± 4
Tissue histamine	37 ± 5	32 ± 4
Provocation	34 ± 5	24 ± 6 **
Mast cells	61 ± 4	58 ± 5
Provocation	58 ± 5	44 ± 5 **
PGE_2	12 ± 3	15 ± 4
Provocation	14 ± 2	12 ± 3
Gastric motility	6 ± 4	9 ± 4
Intestinal motility	9 ± 4	14 ± 5

Plant-based medicaments for increasing the tone and modulating the tone of the smooth muscular organs.

Patent Claims

1. Plant-based medicament having tonicising activity on smooth muscular organs which are atonic or have decreased tone, characterized in that it contains Iberis amara as the sole carrier of the activity.

2. Plant-based medicament having tone-modulating activity on smooth muscular organs which have decreased tone or increased tone, characterized in that it contains Iberis amara, together with one or more other constitutents selected from the group consisting of
Menthae piperitae folium,
Matricariae flos,
Carvi fructus,
Melissae folium, and
Liquiritiae radix,
as the sole carrier of the activity.

3. Plant-based medicament according to Claim 1 or 2, wherein said plant-based medicament comprises a plant extract or its constituents, derived from Iberis amara.

4. Plant-based medicament according to Claim 2, wherein said other constituents are plant extracts.

5. Plant-based medicament according to any one of Claims 1 to 4, wherein said Iberis amara comprises Iberis amara totalis.

6. Plant-based medicament according to any one of Claims 1 to 5, wherein said plant-based medicament contains Iberis amara flowers, Iberis amara seeds, Iberis amara leaves, Iberis amara stalk or Iberis amara roots.

7. Plant-based medicament according to any one of Claims 1 to 6, characterized in that it contains a plant extract comprising about
15 – 40 % by volume of Iberis amara,
10 – 30 % by volume of Menthae piperitae,

20 – 40 % by volume of Matricariae,
10 – 30 % by volume of Carvi fructus,
10 – 30 % by volume of Melissae folium, and
10 – 30 % by volume of Liquiritiae radix.

8. Plant-based medicament according to Claim 7, characterized in that it contains, a plant extract comprising about
15 % by volume of Iberis amara totalis,
10 % by volume of Menthae piperitae folium,
30 % by volume of Matricariae flos,
20 % by volume of Carvi fructus,
15 % by volume of Melissae folium, and
10 % by volume of Liquiritiae radix.

9. Plant-based medicament according to any one of Claims 3, 4, 7 or 8, characterized in that the plant extract is a fresh plant extract.

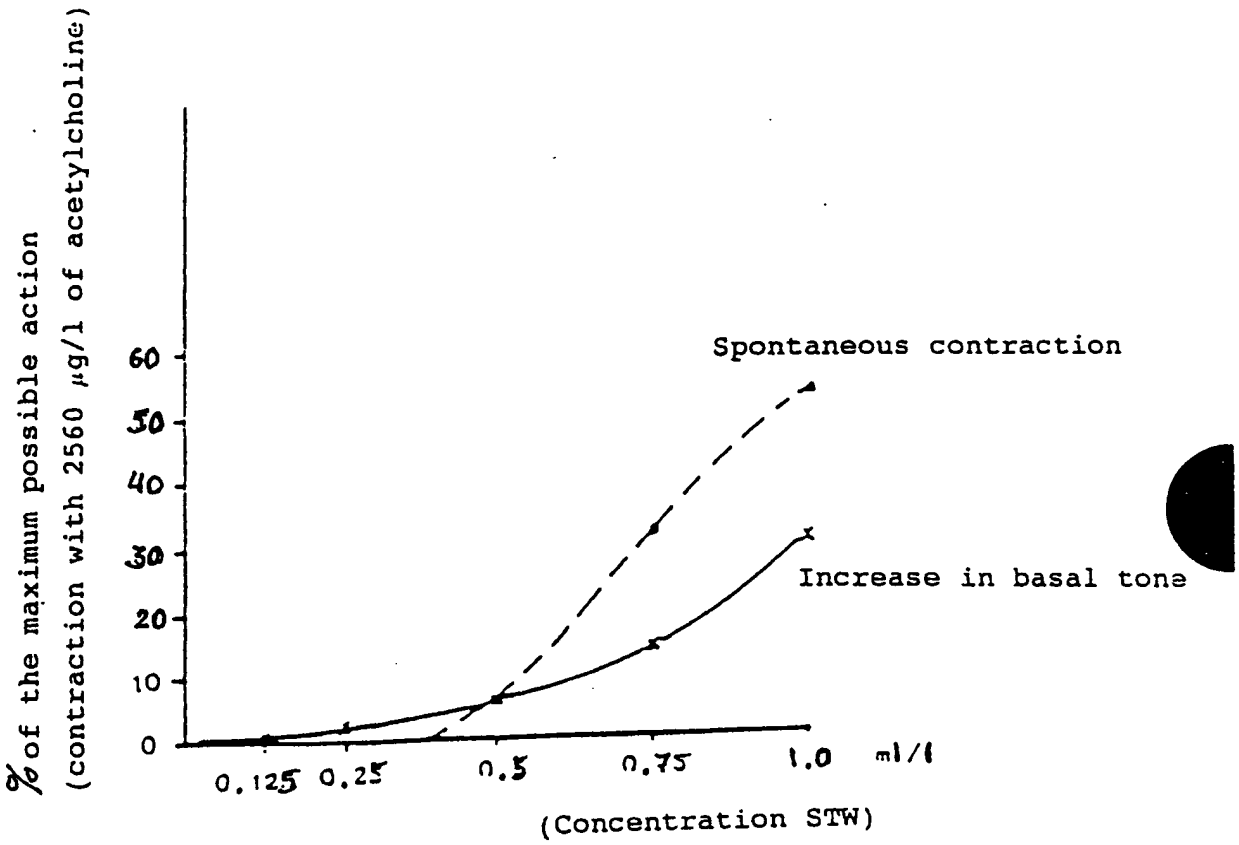
10. Plant-based medicament according to Claim 9, characterized in that in the fresh plant extract the ratio of macerated or percolated plant to the extract is about 3 to 7 by weight.

11. Plant-based medicament according to Claims 1 to 10, characterized in that in the drug extract the ratio of drugs to extract is about 1.5 to 5 by weight.

12. Plant-based medicament according to Claims 1 to 11, characterized in that the extracting agent is ethanol in a final concentration of 30 – 40 % by volume, the remainder being H_2O.

13. Plant-based medicament according to Claim 9, characterized in that in the fresh plant extract the ratio of macerated to percolated plant to the extract is about
6 to 10 by weight.

14. Plant-based medicament according to Claims 1 to 10, characterized in that in the drug extract the ratio of drugs to extract is 3.5 to 10 by weight.



Effect of STW 6 on the tone of resting isolated guinea-pig ileum

Fig. 1

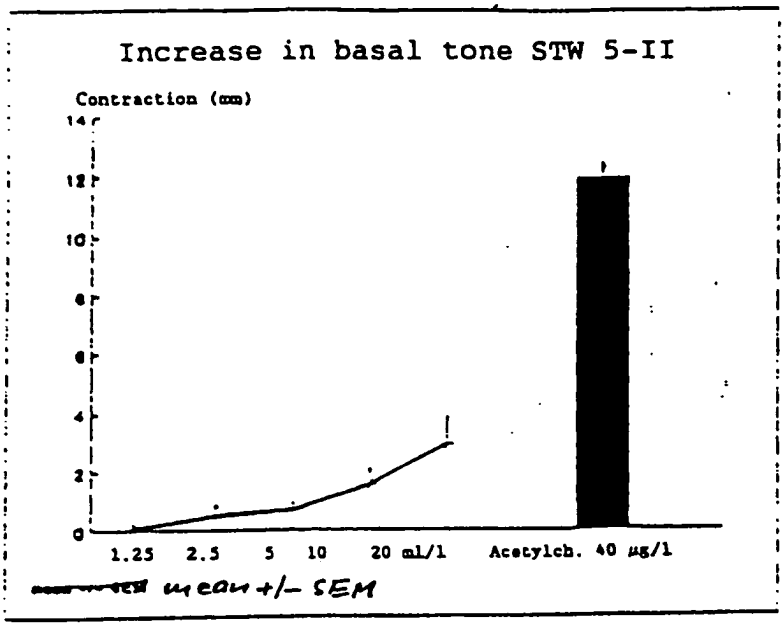

Increase in basal tone STW 5-II
Contraction (mm)
14
12
10
8
6
4
2
0
1.25
2.5
5
10
20 ml/1
Acetylch. 40 µg/1
mean +/- SEM

Fig. 2

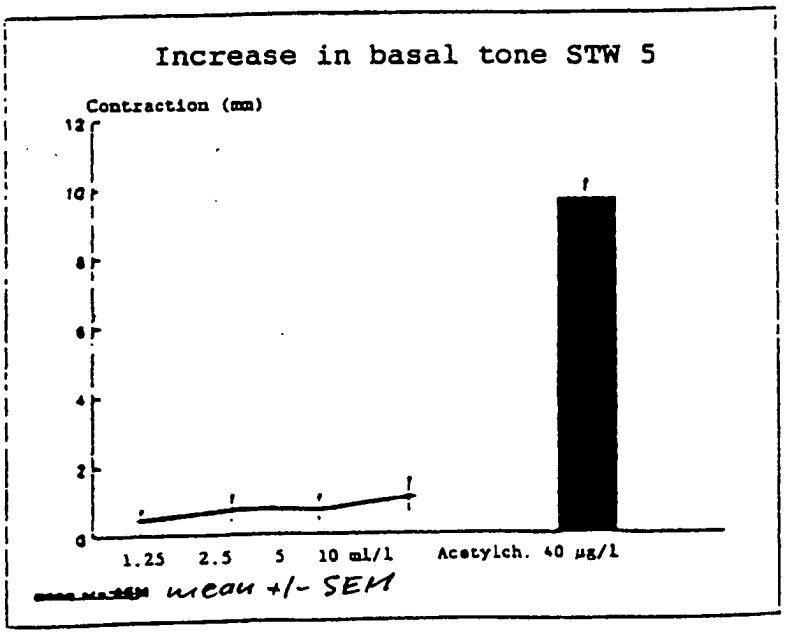

Increase in basal tone STW 5
Contraction (mm)
12
10
8
6
4
2
0
1.25
2.5
5
10 ml/1
Acetylch. 40 µg/1
mean +/- SEM

Fig. 3

STW 5 1.25 ml/l o——o HISTAMINE control x——x Ileum

STW 5-II 1.25 ml/l □——□ n = 6

100,000 µg/l: n = 4

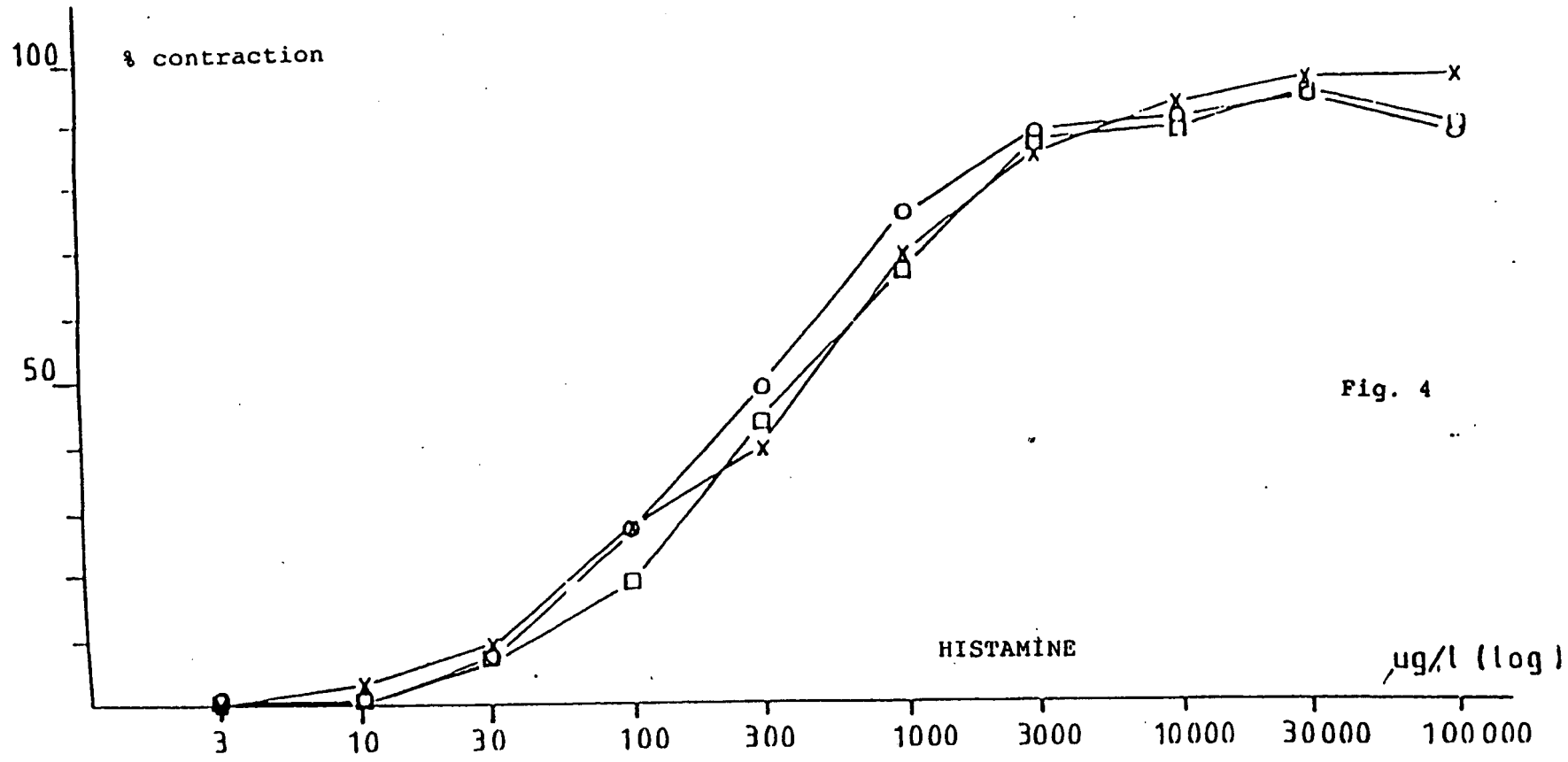


Fig. 4

STW 5 2.5 ml/l o——o

STW 5-II 2.5 ml/l □——□

HISTAMINE control X——X

Ileum

n = 6

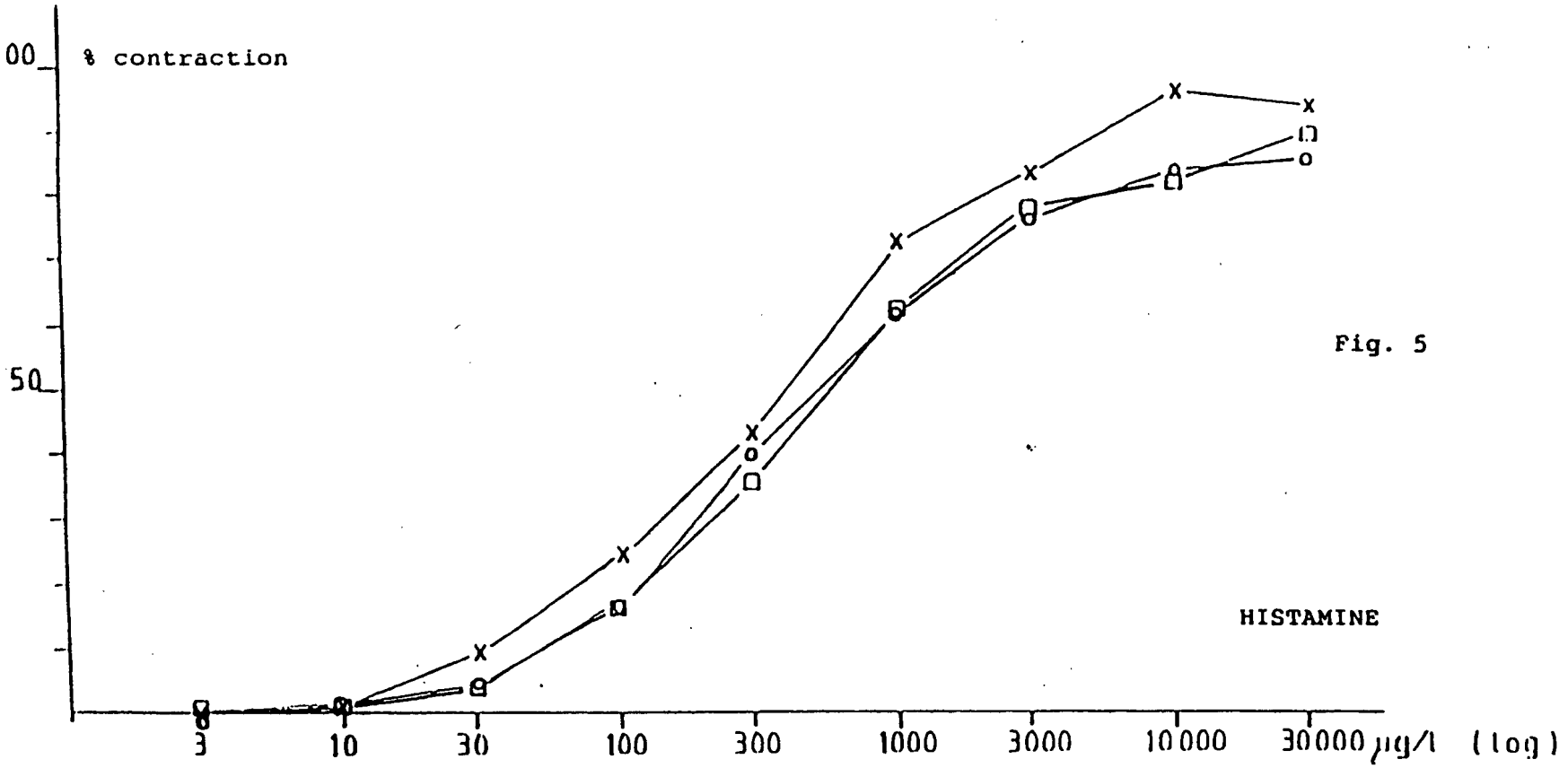


Fig. 5

STW 5 5.0 ml/l o——o

STW 5-II 5.0 ml/l □——□

HISTAMINE control x——x

Ileum

n = 6

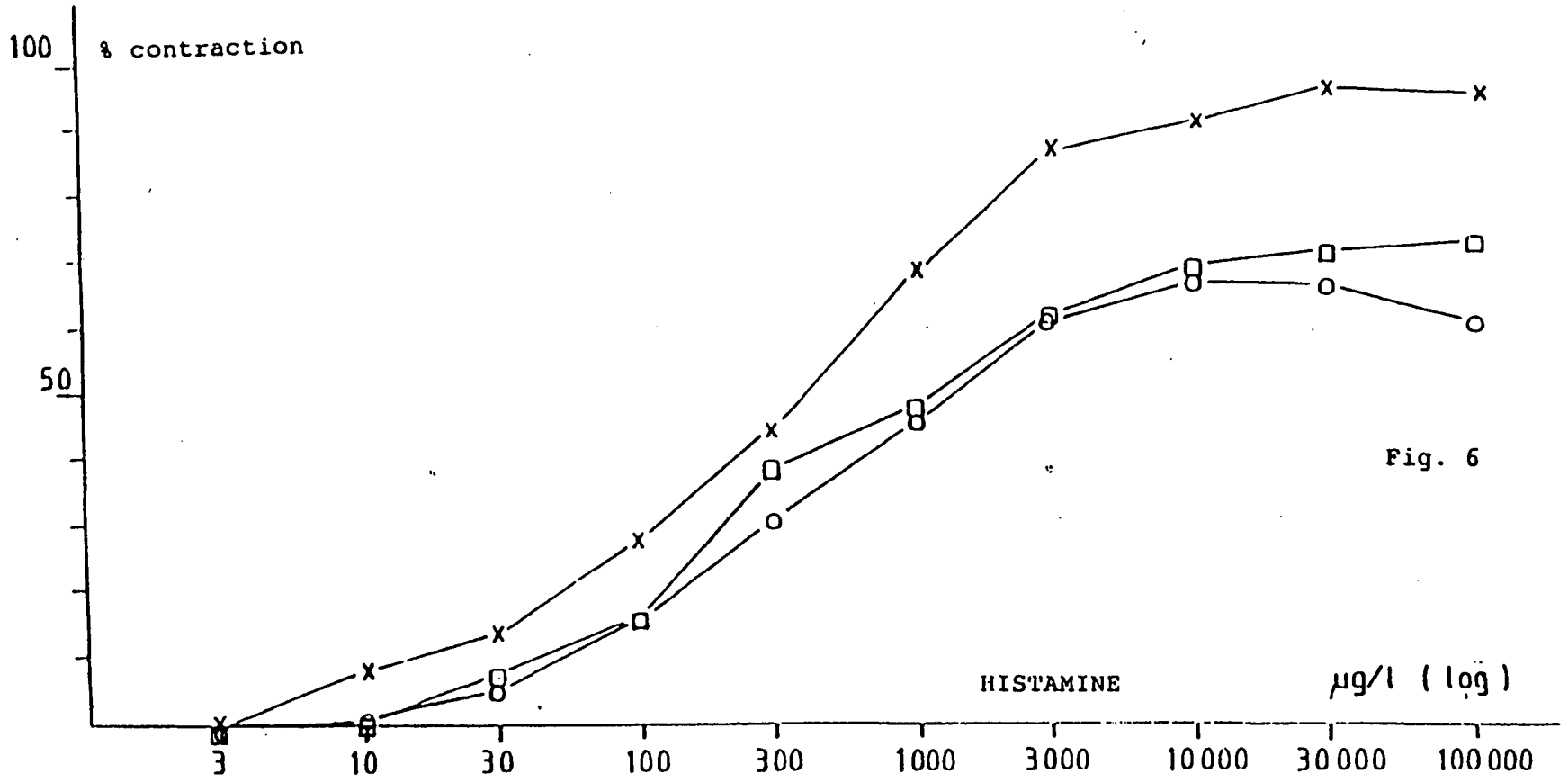


Fig. 6

STW 5 10.0 ml/l o——o

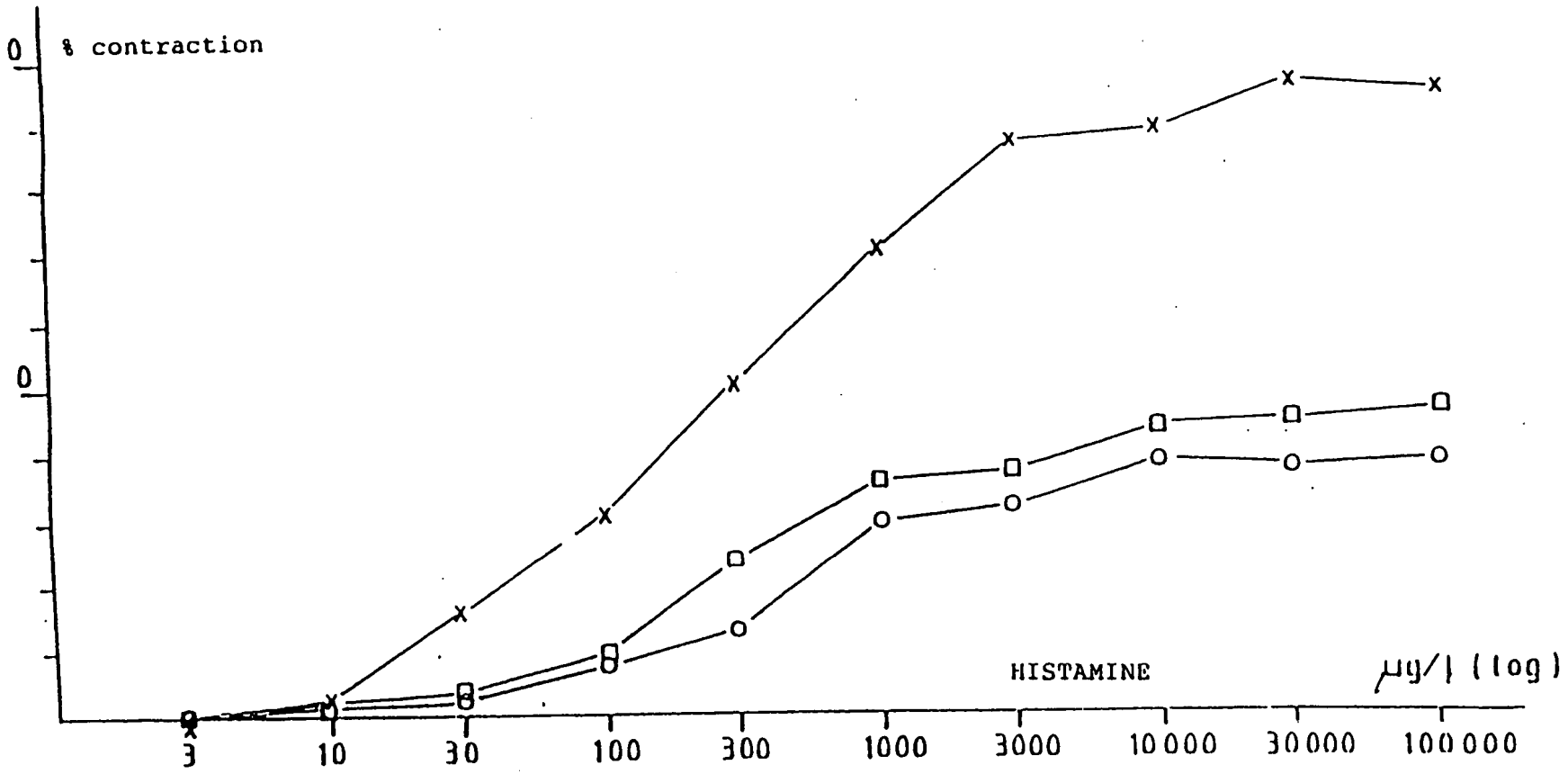
STW 5-II 10.0 ml/l □——□

HISTAMINE control x——x

Ileum

n = 6

Fig. 7



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